BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

REMARKS

Claims 49, 53, and 55 have been amended. Claims 1-59 are pending in the instant application. Support for the amendments to the claims can be found in the specification at, for example, page 65, lines 17-28 and page 54, lines 20-23. No new matter has been added as a result of the above-described amendments. The rejections set forth in the Office Action have been overcome by amendment or are traversed by argument below.

1. Information Disclosure Statement

The Office Action states that certain references listed on the Information Disclosure Statement filed July 25, 2001 were not present, and therefore, have not been considered. Applicants hereby file a Supplemental Information Disclosure Statement listing those references that, due to inadvertent errors or omissions in the Information Disclosure Statement filed July 25, 2001, have not yet been considered. In addition, the Supplemental Information Disclosure Statement lists one reference that was not available at the time the prior Information Disclosure Statement was filed.

2. Objection to the specification

The Office Action contains an objection to the specification because the references to "Figures 6A-6B" and "Figure 7" at pages 6-7 do not match the figures. Applicants have amended the specification so that the references to these figures at pages 6-7 match the figures, and, therefore, respectfully request that this objection be withdrawn.

3. Objection to claim 49 under 37 C.F.R. § 1.75(c)

The Office Action contains an objection to claim 49 under 37 C.F.R. § 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. The Action states that the phrase "the nucleic acid molecule defined in Claim 1" is unclear. Applicants have amended claim 49 to recite instead "the nucleic acid molecule of Claim 1." Applicants contend that the claim 49, as amended, complies with 37 C.F.R. § 1.75(c), and therefore, respectfully request that this ground of rejection be withdrawn.

4. Claim of priority

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive
Chicago, Illinois 60606
(312) 913-0001

The Office Action asserts that the amino acid sequences set forth in SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, and SEQ ID NO: 20 are entitled under 35 U.S.C. § 119(a) to the benefit of the June 21, 1989 filing date of German Patent Application No. P39 20 282.8. The Action also asserts that the amino acid sequence set forth in SEQ ID NO: 2 is entitled under 35 U.S.C. § 119(a) to the benefit of the April 6, 1990 filing date of European Patent Application No. 90106624.1. The Action further asserts that the limitation "not associated with human urinary proteins" is entitled under 35 U.S.C. § 120 to the benefit of the February 23, 2001 filing date of U.S. Application No. 09/792,356.

Although Applicants respectfully disagree with each of the Action's priority determinations, Applicants contend that only the latter determination (*i.e.*, that the limitation "not associated with human urinary proteins" is only entitled to the benefit of the February 23, 2001 filing date of U.S. Application No. 09/792,356) is relevant to the rejections made in the instant Action (*see* discussion in sections 7 and 8 below). Applicants, therefore, address this determination of priority.

Applicants respectfully disagree with the Action's determination that the limitation "not associated with human urinary proteins" is entitled under 35 U.S.C. § 120 only to the benefit of the February 23, 2001 filing date of U.S. Application No. 09/792,356, and on the contrary contend that with respect to this limitation, the instant application is entitled under 35 U.S.C. § 120 to the benefit of the April 20, 1990 filing date of U.S. Application No. 07/511,430 and is entitled under 35 U.S.C. § 119(a) to the benefit of the filing dates of German Patent Application Nos. P39 13 101.7 (filed April 21, 1989) and P39 20 282.8 (filed June 21, 1989) and European Patent Application No. 90106624.1 (filed April 20, 1990). Applicants note first that because the instant application is a continuation application of U.S. Application No. 08/477,639 (filed June 7, 1995), which is a divisional application of U.S. Application No. 08/383,676 (filed February 1, 1995), which is a continuation application of U.S. Application No. 08/153,287 (filed November 17, 1993), which is a continuation application of U.S. Application No. 07/821,750 (filed January 2, 1992), which is a divisional application of U.S. Application No. 07/511,430, the specifications of the instant application and U.S. Application No. 07/511,430 are identical in every respect, so that whatever is disclosed in the instant specification was disclosed identically in the specification of U.S. Application No. 07/511,430.

Applicants next direct the Examiner's attention to page 3, lines 15-22; page 8, lines 22-25;

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive
Chicago, Illinois 60606
(312) 913-0001

page 9, lines 3-10; page 19, line 30 to page 20, line 2; page 36, lines 20-26; and page 78, line 13 to page 80, line 20 of their specification. Applicants contend that one of ordinary skill in the art would understand that these passages provide support for the limitation "not associated with human urinary proteins." Identical support for this limitation can also be found in European Patent Application No. 90106624.1 at page 4, lines 8-15; page 5, lines 23-26; page 6, lines 9-18; page 10, lines 18-23; page 24, lines 9-14; and page 74, line 9 to page 76, line 19. Prior to Applicants' disclosure of the recombinant molecules of the invention, the only method for producing a substantially homogeneous sample of TNF binding protein was to purify the protein from human urine (page 3, lines 15-22 of the instant specification). Only Applicants' invention provided the nucleic acid sequence of TNF binding protein, which was absolutely necessary, in order to recombinantly produce TNF binding protein (page 19, line 30 to page 20, line 2). Applicants disclosed that by introducing into a suitable host organism a construct containing the nucleic acid sequence of TNF binding protein (with a sequence coding for a signal peptide) under the control of a suitable promoter, one of ordinary skill in the art can produce TNF binding protein that is secreted into the cell culture medium (page 36, lines 20-26). In fact, Applicants affirmatively demonstrated such recombinant expression of TNF binding protein in both COS-7 and CHO DUKC BII cells (page 78, line 13 to page 80, line 20). Applicants contend that, in light of the specification's disclosure and knowledge in the art, one of ordinary skill in the art would readily understand that a *substantially* homogeneous TNF binding protein purified from urine could *not* be completely free of human urinary proteins, and that the recombinantly produced TNF binding protein of Applicants' invention must be *inherently and absolutely* free of human urinary proteins. Applicants respectfully contend, therefore, that the applications from which the instant application claims priority provide support for the limitation "not associated with human urinary proteins," and therefore, that this limitation is entitled to the benefit of the earlier filing dates of these applications.

5. Rejections of claims 15-22, 37-40, 43, 44, and 50-59 under 35 U.S.C. § 112, first paragraph

The Office Action asserts a rejection of claims 15-22, 37-40, 43, 44, and 50-59 under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive
Chicago, Illinois 60606
(312) 913-0001

scope with the claims. The Action states that the specification, while being enabling for making and using a recombinant polypeptide comprising the amino acid sequence set forth in any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, or SEQ ID NO: 20, does not reasonably provide enablement for making and using recombinant polypeptide variants of these sequences having at least one conservative amino acid substitution, at least one amino acid substitution at a glycosylation site, at least one amino acid substitution at a proteolytic cleavage site, at least one amino acid substitution at a cysteine residue, at least one amino acid deletion, at least one amino acid insertion, or a combination of these modifications. The Action also states that in the absence of information concerning those residues in the amino acid sequence of SEQ ID NO: 4 that are essential for its biological activity and structural integrity, a person skilled in the art would have to resort to a substantial amount of undue experimentation in the form of insertional, deletional, and substitutional mutation analysis before that person could begin to rationally design a functional TNF binding protein variant.

The Action also asserts a rejection of the claims under 35 U.S.C. § 112, first paragraph, in so far as the claims encompass an isolated protein other than a recombinant polypeptide comprising the amino acid sequence set forth in any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, or SEQ ID NO: 20, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Action states that because the specification merely discloses one polypeptide sequence, the written description does not support the claimed scope and does not fulfill the written description requirements of 35 U.S.C. § 112, first paragraph.

Applicants respectfully disagree with the assertion that the specification does not enable a skilled artisan to use the invention commensurate in scope with the claims, or that that the specification fails to reasonably convey to a skilled artisan that the inventors had possession of the claimed invention at the time the application was filed. Applicants note that the specification sets forth the amino acid sequences of a TNF receptor polypeptide (page 5, lines 7-39) and a 161 amino acid portion of this sequence having the ability to bind TNF (page 5, line 45 to page 6, line 3). The specification also discloses that the first 29 amino acid residues of the TNF receptor polypeptide

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive
Chicago, Illinois 60606
(312) 913-0001

constitute the signal peptide (page 21, line 35 to page 22, line 2), and that amino acid residues 30-40 and 202-211 are proteolytically cleaved from the TNF receptor to form the TNF binding protein (page 22, lines 11-12 and page 23, lines 27-29). The specification teaches that techniques for making conservative substitutions are well known in the art (page 14, lines 13-15), and provides a list of exemplary conservative substitutions (page 15, Table 1). Applicants contend that they are under no duty under the statute to enumerate all of the species disclosed generically in their specification, particularly where, as here, the structure of the native molecule is disclosed, the types of variants of said structure are generically disclosed, and a functional property of the claimed molecule (TNF binding activity) and assays to assess species for said property are disclosed. The specification also teaches the location of glycosylation sites (page 22, lines 16-19), proteolytic cleavage sites (page 22, lines 26-28 and page 23, lines 27-29), and cysteine residues (SEQ ID NO: 2), wherein amino substitutions can be made.

Applicants also respectfully disagree with the Action's assertion that the claims of the instant application are analogous to claim 7 of U.S. Patent No. 4,703,008 (the '008 patent), which was held invalid for lack of enablement in *Amgen Inc. v. Chugai Pharmaceuticals Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991). In that case, the Federal Circuit noted that for inventions directed to DNA sequences, to enable one skilled in the art to carry out the invention commensurate with the scope of the claims, the specification must disclose how to make and use enough sequences to justify the grant of the claims sought. *Amgen Inc.*, 927 F.2d at 1213. The Court determined that the specification of the '008 patent was insufficient to enable one of ordinary skill in the art to make and use the claimed invention because it disclosed how to make and use only a few of the nearly infinite number of erythropoietin variants encompassed by claim 7 (the trial court had found that a skilled artisan, by making substitutions at only three positions in the erythropoietin sequence, could generate over a million different erythropoietin variants). *Id.* Because the disclosure was limited to only a few erythropoietin variants, the specification failed to disclose how to make and use enough sequences to justify a claim encompassing *any* DNA sequence that encodes a polypeptide having erythropoietin-like activity. *Amgen Inc.*, 927 F.2d at 1213-14. In contrast, the instant application discloses, for example, a 161 amino acid portion of the TNF receptor polypeptide that possesses the ability to bind TNF; the locations of glycosylation sites, proteolytic cleavage sites, and cysteine residues; and a list of exemplary conservative substitutions. In addition, the claims of the instant

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive
Chicago, Illinois 60606
(312) 913-0001

application are not directed to methods that use *any* DNA sequence that encodes a polypeptide having the ability to bind TNF, but rather are directed to methods that use sequences which are closely related to the disclosed TNF binding sequences of the invention. Applicants respectfully contend that because the specification discloses how to make and use enough sequences and enables one skilled in the art to carry out the invention commensurate with the scope of the claims, the claims of the instant application are not analogous to claim 7 of the '008 patent.

Applicants also note that independent claims 1, 14, 15, 23, 36, 37, 41-44, and 49 contain an explicit limitation to encompass only those molecules that possess a particular activity, namely, the *ability to bind TNF*. The specification defines the "ability to bind TNF" as "the ability of a protein to bind to TNF-α in such a way that TNF-α is prevented from binding to the functional part of the receptor and the activity of TNF-α in humans or animals is inhibited or prevented altogether" (page 17, lines 23-28). In view of the explicit limitation that the claimed molecules possess the ability to bind TNF, Applicants also respectfully disagree with the Action's assertion regarding the specie of substituted molecule having conservative substitutions at every amino acid position. The Action asserts that by making conservative amino acid substitutions at every residue, one of ordinary skill in the art can prepare a polypeptide comprising an amino acid sequence that differs from the polypeptides disclosed in the instant specification and expect it to have the same functions as the polypeptides disclosed in the instant specification. Applicants contend that one of ordinary skill in the art would appreciate that a polypeptide prepared by making conservative amino acid substitutions at every residue would not have the same functions as the unsubstituted polypeptide. Applicants contend that in view of the instant specification's teachings (as discussed above), one of ordinary skill in the art would readily be able to determine which TNF binding protein variants have the ability to bind TNF, and therefore, that it would not require undue experimentation for one of ordinary skill in the art to determine which TNF binding protein variants fall within the scope of the instant claims.

Applicants contend that the specification conveys to one of ordinary skill in the art that the inventors had possession of the claimed invention, and therefore, respectfully request that the rejections under 35 U.S.C. § 112, first paragraph, be withdrawn.

6. Rejections of claims 49 and 53-57 under 35 U.S.C. § 112, second paragraph

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive
Chicago, Illinois 60606
(312) 913-0001

The Office Action asserts a rejection of claims 49 and 53-57 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The Action first asserts that there is insufficient antecedent basis in claims 53 and 55 for the term "cell line." Applicants respectfully contend that because claim 53 has been amended to recite that "the non-human cell is a prokaryotic cell" and claim 55 has been amended to recite that "the non-human cell is a eukaryotic cell," this ground of rejection should be withdrawn.

The Action also asserts that claim 49 is indefinite for reciting "[a] nucleic acid that hybridizes under moderately or highly stringent conditions," because the specification does not define any hybridization conditions, and the term "moderately or highly stringent" does not clearly set forth the metes and bounds of the patent protection desired.

Applicants respectfully disagree with the assertion that the specification does not define any hybridization conditions. In fact, the specification discloses that cDNA clones containing TNF binding protein coding sequences were isolated from a fibrosarcoma cDNA library by hybridization for 16 hours at 65°C using a 0.4 kb probe isolated from the TNF-α induced fibrosarcoma cDNA library in a hybridization solution composed of 6x SSC, 5X Denhardt's, and 0.1% SDS (page 65, lines 17-28; page 54, lines 20-23). However, in an effort to expedite prosecution of the instant application, Applicants have amended claim 49 to recite "[a] nucleic acid that hybridizes to the complement of the nucleic acid molecule of Claim 40 at 65°C in a hybridization buffer comprising 6x SSC and 0.1% SDS." Applicants contend that amended claim 49 satisfies the definiteness requirement of § 112, second paragraph, and therefore, respectfully request that this ground of rejection be withdrawn.

Applicants respectfully contend that rejections based on 35 U.S.C. § 112, second paragraph, have been overcome by amendment or traversed by argument, and request that the Examiner withdraw all rejections made on this basis.

7. Rejection of claims 15, 22, 37-40, and 43-50 under 35 U.S.C. § 102

The Office Action asserts a rejection of claims 15, 22, 37-40, and 43-50 under 35 U.S.C. § 102(a) as being anticipated by European Patent Application No. 0 308 378 (Wallach *et al.*, published March 22, 1989), contending that this reference discloses the purification of a TNF-inhibiting protein

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive
Chicago, Illinois 60606
(312) 913-0001

that the instant specification describes as being identical to a TNF binding protein of the instant invention. The Action states that while the amino acid sequences set forth in SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, and SEQ ID NO: 20 comprise up to 21 more amino acid residues than the soluble TNF binding protein of Wallach *et al.*, this reference encompasses a TNF binding protein of the instant invention comprising a C-terminal deletion. The Action also states that while the amino acid sequences set forth in SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, and SEQ ID NO: 20 are not taught by Wallach *et al.*, the amino acid sequence of a protein is an intrinsic property of the protein. The Action also states that because the TNF-inhibiting protein of Wallach *et al.* has been extensively purified, it is no longer associated with urinary proteins. The Action further states that the Wallach *et al.* reference discloses that TNF binding proteins may be used in treating any condition where there is an over-production of endogenous TNF, such as in cases of septic shock, cachexia, graft-versus-host reactions, and autoimmune diseases like rheumatoid arthritis. Applicants traverse this rejection.

To support a rejection under 35 U.S.C. § 102, "the four corners of a single, prior art document [must] describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *In re Paulsen*, 30 F.3d 1475, 1479 (Fed. Cir. 1994). The exclusion of even a single claimed element, no matter how insubstantial or obvious, from a reference is enough to negate anticipation. *Connell v. Sears, Roebuck & Co.*, 220 U.S.P.Q. (BNA) 193, 198 (Fed. Cir. 1983). The identical invention must also be shown in the single prior art reference in as complete detail as contained in the application against which the reference is cited. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). Moreover, the prior art reference must be enabling, thus placing the claimed invention in the possession of the public. *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 88 (D. Mass 2001) (citing *Akzo N.V. v. United States Int'l Trade Comm'n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986)).

Applicants note that European Patent Application No. 0 308 378 provides only a *partial, incomplete* amino acid sequence of a TNF inhibitory protein – and no nucleotide sequence whatsoever (*see* page 3, line 61; page 8, line 21; and page 9, line 33). Applicants contend that

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive
Chicago, Illinois 60606
(312) 913-0001

because the Wallach *et al.* reference does not disclose the complete nucleotide and amino acid sequence of TNF binding protein in EP 0 308 378 – and in fact, discloses *only* fourteen of the first sixteen amino acid residues of a TNF inhibitory protein – this reference *cannot* anticipate methods for ameliorating the harmful effects of TNF in an animal, comprising administering to an animal in need of such treatment a therapeutically effective amount of a recombinant polypeptide having the ability to bind TNF, wherein said polypeptide is not associated with human urinary proteins, and wherein said polypeptide comprises the amino acid sequence as set forth in any of SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, residues 2 through 183 of SEQ ID NO: 10, residues 2 through 173 of SEQ ID NO: 16, or residues 2 through 172 of SEQ ID NO: 20.

Applicants also note that the Wallach *et al.* reference discloses a TNF binding protein purified from human urine by use of dialysis, ion exchange chromatography, and reverse phase high pressure liquid chromatography. Applicants contend that because the TNF binding protein disclosed by Wallach *et al.* is purified from urine, this reference *cannot* anticipate methods that use a *recombinant* polypeptide having the ability to bind TNF, wherein said polypeptide is *not associated with human urinary proteins*. Applicants respectfully contend that the Wallach *et al.* reference does not and cannot teach such a TNF binding protein, since the urine-derived product is inherently associated with such human urinary proteins (in fact, at page 3, lines 49-50, Wallach *et al.* refer to their urine-derived TNF binding protein as merely "substantially free of proteinaceous impurities" rather than as completely and absolutely free of human urinary proteins). Moreover, Applicants contend that the assertion that methods that use a purified TNF binding protein anticipate methods that use a recombinant TNF binding protein is entirely analogous to the assertion, made in *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, that erythropoietin purified from patients with anemia anticipates recombinant erythropoietin. 126 F. Supp. 2d 69, 88 (D. Mass 2001) (holding that a reference disclosing erythropoietin purified from patients with anemia does *not* anticipate claims to recombinant erythropoietin).

Applicants contend that European Patent Application No. 0 308 378 cannot anticipate the claimed methods of the present application, and therefore, respectfully request that the rejection of claims 15, 22, 37-40, and 43-50 on 35 U.S.C. § 102 grounds be withdrawn.

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive
Chicago, Illinois 60606
(312) 913-0001

8. Rejection of claims 15, 22, and 49 under 35 U.S.C. § 103

The Office Action asserts a rejection of claims 15, 22, and 49 under 35 U.S.C. § 103(a) as being unpatentable over Olsson *et al.*, 1989, *Eur. J. Haematol.* 42:270-75, and further in view of European Patent Application No. 0 308 378 (Wallach *et al.*, published March 22, 1989). The Action states that because the Olsson *et al.* reference discloses the isolation of a TNF binding protein comprising an amino-terminal sequence (*i.e.*, Asp-Ser-Val-Xaa-Pro-Gln-Gly-Lys-Tyr-Ile-His-Pro-Gln-Val-Asn-Ser-Ile-Xaa-Lys-Thr) which differs from the amino acid sequence set forth in SEQ ID NO: 2 at only two positions, this reference encompasses a TNF binding protein of the instant invention comprising at least one amino acid substitution and a C-terminal deletion. The Action also states that while the Olsson *et al.* reference does not disclose a method of treatment comprising administering a TNF binding protein of the instant invention, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the TNF binding protein disclosed in the Olsson *et al.* reference to treat the TNF-mediated disorders disclosed in the Wallach *et al.* reference. Applicants traverse this rejection.

The claims of the instant application recite methods for ameliorating the harmful effects of TNF in an animal, comprising administering to an animal in need of such treatment a therapeutically effective amount of a *recombinant* polypeptide having the ability to bind TNF, wherein said polypeptide is *not associated with human urinary proteins*. Applicants note that the Olsson *et al.* reference discloses a TNF binding protein purified from the urine of patients with chronic renal failure by use of ion exchange chromatography, affinity chromatography on TNF-Sepharose, and reverse phase chromatography. Applicants contend that because the TNF binding protein disclosed by Olsson *et al.* is purified from urine, this reference does *not* teach a recombinant TNF binding protein that is not associated with human urinary proteins, since the urine-derived product of Olsson *et al.* is inherently associated with such human urinary proteins. Applicants also note that the Olsson *et al.* reference does not disclose the complete nucleotide and amino acid sequence of TNF binding protein – and in fact, discloses *only* eighteen of the first twenty amino acid residues of a TNF inhibitory protein. Applicants contend that it would not have been *prima facie* obvious to one of ordinary skill in the art to use the TNF binding protein disclosed by Olsson *et al.*, and purified from urine, to practice the claimed methods of the invention using a recombinant polypeptide having the ability to bind TNF, wherein said polypeptide is not associated with human urinary proteins.

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive
Chicago, Illinois 60606
(312) 913-0001

Applicants, therefore respectfully request that the rejection of claims 15, 22, and 49 on 35 U.S.C. § 103 grounds be withdrawn.

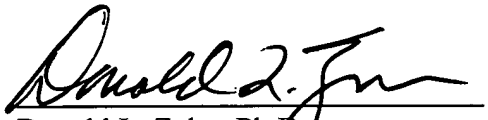
CONCLUSIONS

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended. Allowance of the claims is thereby respectfully solicited.

If Examiner O'Hara believes it to be helpful, she is invited to contact the undersigned representative by telephone at 312-913-0001.

Respectfully submitted,
McDonnell Boehnen Hulbert & Berghoff

Dated: June 30, 2003

By: 
Donald L. Zuhn, Ph.D.
Reg. No. 48,710

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive
Chicago, Illinois 60606
(312) 913-0001